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Unitization supports lasting performance and generalization on a relational memory task: Evidence from a previously undocumented developmental amnesic case

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ABSTRACT

Recently, the amnesic case D.A. was shown to circumvent his relational memory impairments, as observed in the transverse patterning (TP) task, using a self-generated unitization strategy, and such performance benefits were maintained over extended delays (Ryan et al., 2013). "Unitization" encourages fusing of distinct items, through an action, into a single unit from which the relations among the items may then be derived. Here, we provide the first documentation of the developmental amnesic case, N.C., who presents with relatively circumscribed lesions to the extended hippocampal system, and with impaired episodic memory. Despite impairments on standard versions of TP, N.C. benefited from unitization, showed evidence of transfer to novel stimuli, and maintained his performance over extended delays. These findings suggest that self-generation is not a requirement for the successful implementation of unitization, and further provides the first evidence of rapid transfer and long-lasting success of a learning strategy in a human amnesic case.

1. Introduction

Amnesia is often characterized by a pervasive impairment in the ability to bind together separate pieces of information to form novel relations (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001; Moses and Ryan, 2006; Ryan et al., 2000). The transverse patterning (TP) task is often used to examine the role of the hippocampus in forming these novel relations. In TP, the relations among three items are learned, where each item wins in the context of one of the other items and loses in the context of the other item, similar to the childhood game of "rock, paper, scissors". Humans (Moses et al., 2008; Rickard and Grafman, 1998; Rickard et al., 2006) and non-human animals (Alvarado and Bachevalier, 2005; Alvarado and Rudy, 1995; Driscoll et al., 2005, but see Bussey et al., 1998; Saksida et al., 2006) show impaired TP performance following hippocampal lesions.

Despite the relational memory impairments typically observed in amnesic cases, we have recently demonstrated that a unitization strategy can be used to compensate for such deficits (Ryan et al., 2013). An amnesic person with bilateral damage to the medial temporal lobe (MTL), D.A., reported using a self-generated strategy in TP, in which he imagined pairs of items interacting with one another in order to determine the winner. Using unitization, D.A. was able to learn multiple sets of novel relations and retain them over considerable delays (e.g., months). Despite D.A.'s improved performance with unitization, two other acquired amnesic cases with MTL damage, K.C. and R.F.R., did not show such improvements. We have speculated that differences in improvements with unitization across patients are likely related to differences in their patterns of damage. D.A. has bilateral damage MTL damage affecting his hippocampus, perirhinal cortex, and parahippocampal cortex, with additional right-sided damage to his entorhinal cortex as well as the anterior temporal lobe. In contrast, K.C. and R.F.R. both have more diffuse patterns of damage that includes the anterior temporal lobes bilaterally. Given the differing patterns of damage across cases, it remains unclear whether other amnesic cases can benefit from D.A.'s self-generated strategy. Specifically, unitization may only support behavior if it is self-generated. However, given K.C.'s and R.F.R.'s extensive cortical damage, it is difficult to ascertain whether performance benefits were not observed because they did not self-generate the

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unitization strategy, or because they have more diffused patterns of damage. Specifically, K.C. and R.F.R. may not have benefited from unitization because their damage extends to areas which may be necessary for the underlying processing mechanisms that support unitization, such as the left anterior temporal lobe (see Ryan et al., 2013 for a more in depth discussion).

To investigate the potential utility of a unitization strategy beyond D.A., we report here the first documentation of the developmental amnesic case, N.C., whose damage is limited to the extended hippocampal system (Aggleton and Brown, 1999), including the mediodorsal nuclei of the thalamus bilaterally and volume reductions in the right fornix and both mammillary bodies. N.C. has a considerably different pathology from D.A., K.C., and R.F.R, yet he presents with a classic neuropsychological profile of episodic amnesia. We investigated whether N.C. would show performance benefits from unitization, despite the absence of self-generation of the strategy, and whether he would be able to transfer the unitization strategy to novel problem sets. N.C.'s demonstration of successful and lasting performance provides compelling evidence of rapid and lasting transfer in an amnesic case, and underscores the importance of replication, particularly when relying on the case study method to inform our understanding of learning strategies and of the brain–behavior relationship (Rosenbaum et al., 2014).

2. Methods

2.1. Amnesic case

N.C. is a young right-handed male with 14 years of education, having completed high school and 1 year of technical college. He was aged 19 at the time of the first two sessions and aged 20 for the remainder of the sessions. At approximately 10 days of age, N.

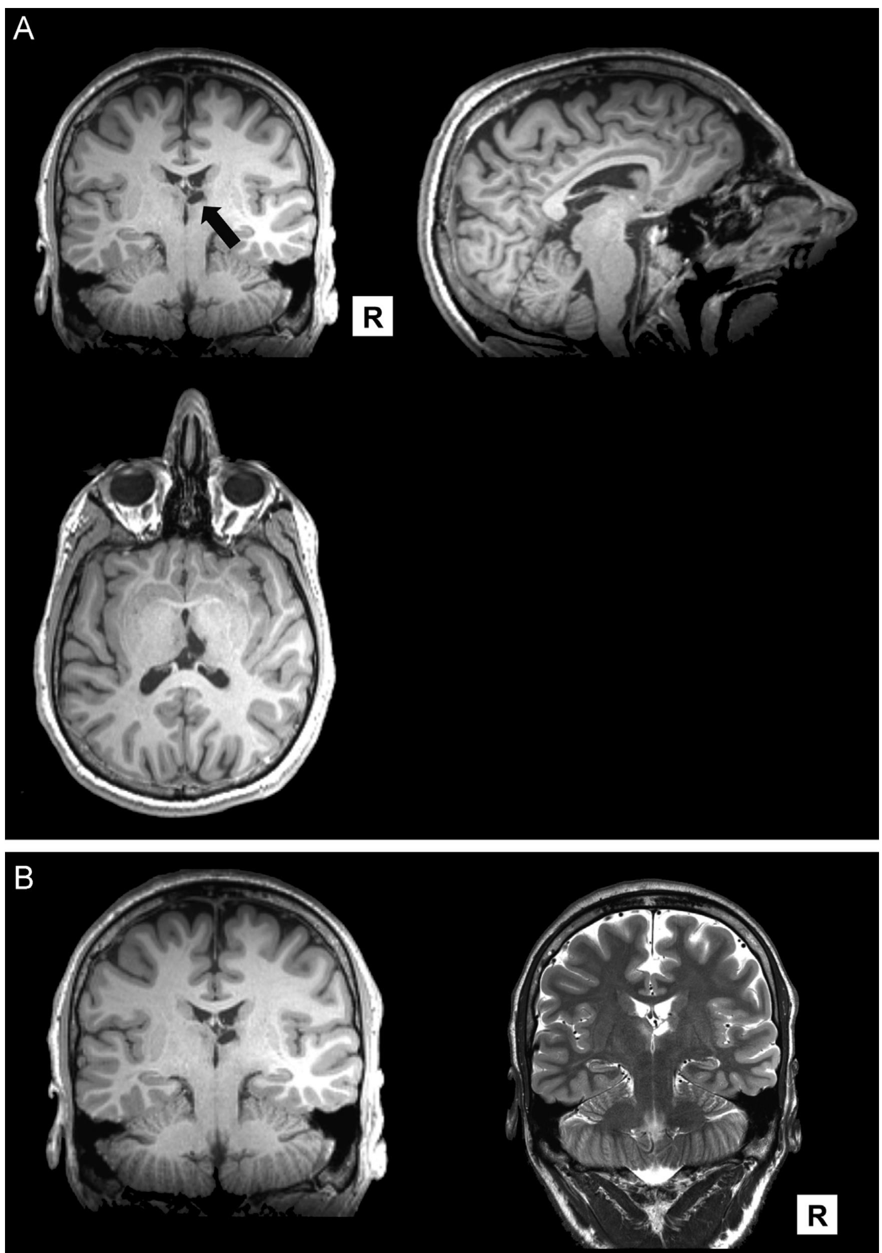

Fig. 1. (A) T1 weighted MRI scans of N.C., with arrow pointing to his right thalamic lesion. (B) T1 weighted and T2 weighted MRI scans (left and right, respectively) showing that N.C.'s lesion shows slightly hypointense on the T1-weighted image and hyperintense on the coronal T2-weighted image.

C. experienced a thalamic stroke, which primarily affected the mediodorsal nucleus of the thalamus bilaterally. Follow-up MRI scans conducted in 2012, analyzed by a radiologist, confirmed an old infarct in the right medial superior thalamus and contralaterally in the left thalamus (see Fig. 1b). The infarct on the right side is predominantly in the mediodorsal nucleus but partially extends into the anterior nucleus. The lesion on the left appears to be limited to the mediodorsal nucleus. N.C.'s right fornix is noticeably atrophic, and his mammillary bodies are reduced in size, especially on the right. His left lateral ventricle is larger than the right, and there are white matter changes along the left lateral ventricle and also in the left temporal lobe, with the inferior longitudinal fasciculus most involved.

2.2. Neuropsychological tests and results

An updated neuropsychological evaluation was performed when NC was 20 years old. Testing results confirmed that in the context of average intelligence, he was severely impaired on tests of delayed recall for both verbal and nonverbal material. He also performed below expected levels on tests of working memory and more complex aspects of visuospatial processing (e.g., recognizing faces, integrating details into a complex figure). In contrast, his performance was largely intact on measures of semantic knowledge, language, processing speed, and executive function (see Table 1).

2.3. Apparatus and stimuli

The apparatus and stimuli were similar to those used in our prior work (Ryan et al., 2013). The experiment was programmed using E-prime 1.1, and the stimuli were presented on a 19-in. monitor. N.C. responded using the keys “P” and “Q” on a standard keyboard. Each of the 11 experimental conditions consisted of three unique stimuli (see Fig. 2). In the initial sessions, N.C. was trained on five conditions: Rock–Paper–Scissors (RPS), Geometric Shapes, Abstract Shapes, Geometric Shapes-Unitized, and Abstract Shapes-Unitized, which we will refer to as the original conditions. These conditions were the same conditions that D.A., K.C., and R.F. R. had been trained on in prior work (Ryan et al., 2013), and differed in the extent to which the objects and the relations were known before the experimental session. The conditions also differed in the training procedures (standard versus unitized, outlined below). The RPS condition contained known objects for which the relations were also known before the experimental session. The RPS stimuli depict the hand game in which rock crushes scissors, scissors cut paper, and paper covers rock. The Geometric Shapes and Geometric Shapes-Unitized conditions contained known objects, but whose relations were unknown prior to training. The Abstract Shapes and Abstract Shapes-Unitized conditions contained unknown objects whose relations were also unknown prior to training. In later sessions, N.C. was trained and tested on five novel sets of stimuli, which are referred to as the transfer conditions and one novel set of stimuli in an elemental learning condition. Three transfer conditions consisted of unknown objects whose relations were unknown prior to training (Abstract Objects-Transfer #1, Abstract Objects-Transfer #2, and Abstract Objects-Transfer #3), and the remaining two transfer conditions consisted of known objects whose relations were unknown prior to training (Geometric Shapes-Transfer #1 and Geometric Shapes-Transfer #2). The elemental learning condition (Geometric Shapes-Elemental) also consisted of known objects.

2.4. Procedure

An overview of the experimental sessions and rationale for

Table 1
Neuropsychological profile of N.C.

Test	Normed Score
General intelligence	
WAIS-IV: full scale IQ (standard score)[a]	94
Verbal comprehension index	101
Perceptual reasoning index	106
Working memory index	76[f]
Processing speed index	91
Semantic knowledge	
WAIS-IV vocabulary (scaled score)[a]	10
Language production	
Boston naming test (percentile)[b]	39th
Semantic fluency (animals) (z-score)[c]	1.47
Anterograde memory	
WMS-IV logical memory	
Logical memory I: immediate recall (scaled score)	7
Logical memory II: delayed recall (scaled score)	2[f]
Logical memory II: recognition (percentile)	3–9th[f]
California verbal learning test-II	
Total trials 1 – 5 (t score)	29[f]
Short delay free recall (z-score)	−2.5[f]
Short delay cued recall (z-score)	−1.5[f]
Long delay free recall (z-score)	−2.5[f]
Long delay cued recall (z-score)	−3[f]
Learning (z-score)	−1.5[f]
Total intrusions (z-score)[e]	5[f]
Total repetitions (z-score)[e]	1.5[f]
Recognition (hits) (z-score)	0.5
Recognition (false positives) (z-score)	3[f]
Discrimination	−1.5[f]
Rey–Osterrieth complex figure (t score)	
Immediate recall	< 20[f]
Delayed recall	< 20[f]
Processing speed	
WASI-IV coding[a]	7
WASI-IV symbol search[a]	10
Visuospatial function	
WAIS-IV block design[a]	13
Rey–Osterrieth complex design-copy (percentile)	11 –16th
Judgment of line orientation (percentile)	72nd
Benton facial recognition test	Borderline
Working memory	
WAIS-IV letter-number sequencing[a]	6
WAIS-IV digit span[a]	5[f]
Attention and executive function	
Trail making test (z-score)[d]	
Part A (sec)	−0.74
Part B (sec)	−0.95
Phonemic fluency (FAS) (z-score)[c]	0.31
WAIS-IV similarities (scaled score)[a]	10
WAIS-IV matrix reasoning (scaled score)[a]	11

WAIS-IV, Wechsler Adult Intelligence Scale–IV; WMS-IV, Wechsler Memory Scale–IV;

[a] Canadian Norms,
[b] in house norms,
[c] Tombaugh et al. (1999),
[d] Tombaugh (2004),
[e] lower scores indicate better performance, and
[f] borderline/impaired performance.

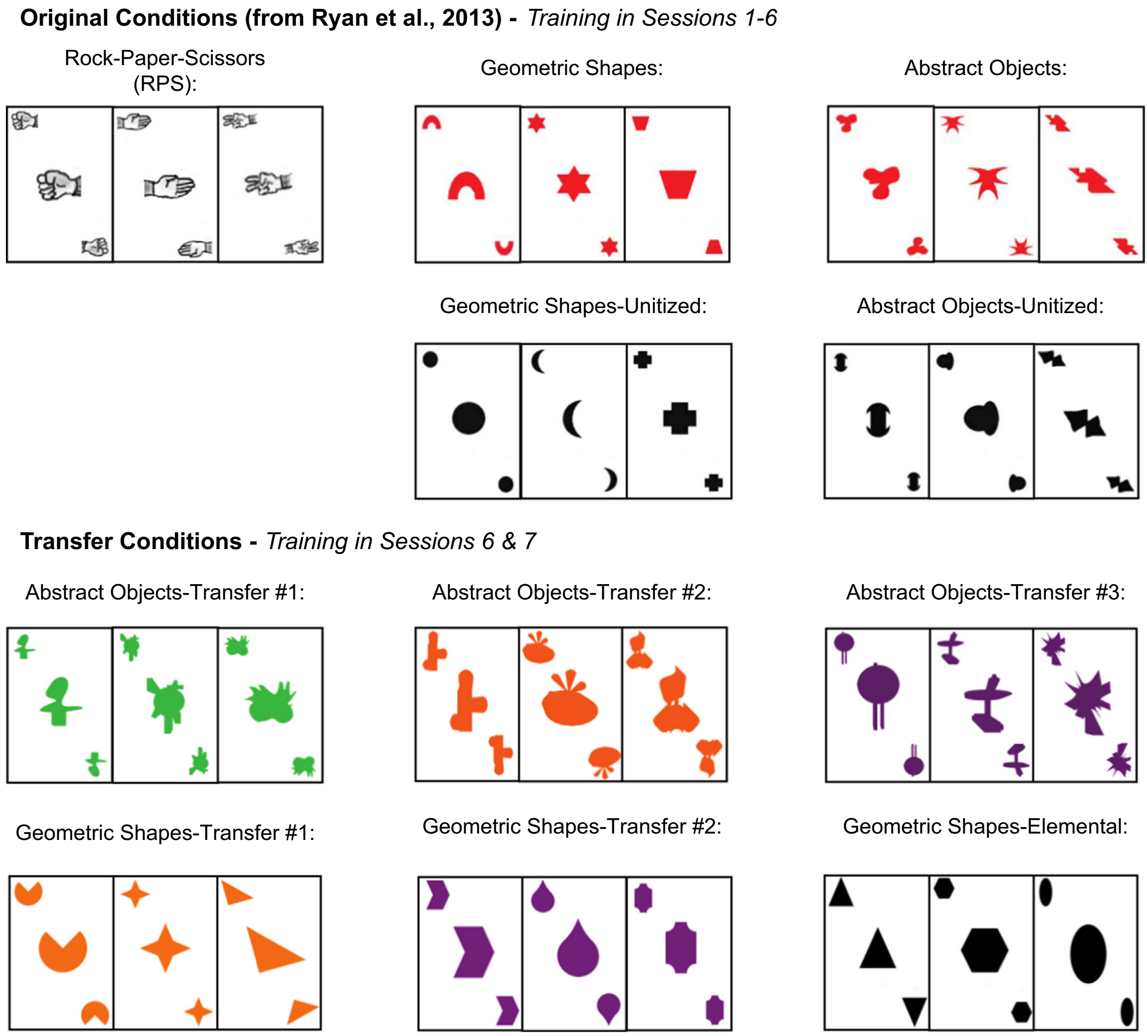

Fig. 2. Stimuli used in the original and transfer transverse patterning conditions and elemental condition.

procedural differences between sessions is provided in Table 2.

N.C. was trained and tested using both standard and unitized training procedures (Ryan et al., 2013) on the relations among three items within each condition. The relations among the items in each condition were A+B−, B+C−, and C+A− for all conditions except for the Geometric Shapes-Elemental condition, which had a hierarchy of relations (A > B > C).

Below we first describe the standard training procedures, followed by the unitization training procedures. Standard training was applied in all conditions not otherwise marked with "Unitized" in the moniker (e.g., Geometric Shapes-Unitized). For all conditions, N.C. was not informed of any of the relations among the stimuli prior to the session. Note that although N.C. was not informed of the relations prior to training in all sessions, he demonstrated awareness that the relations he was tested on were RPS-like in all sessions after Session 3. N.C. was required to learn by trial and error. On each trial N.C. was shown two objects and he was asked to pick one that "wins". The computer provided feedback as to whether he was doing the task correctly. If he picked the correct object, he would see a happy-face cartoon and the caption "Good Job!" and if he picked the incorrect object he would see an angry-face cartoon and the caption "Wrong!" (Fig. 3).

2.4.1 Standard training

For all conditions, training involved five stages. Stage 1 consisted of 10 trials of one pair (AB × 10), followed by 10 trials of the next pair (BC × 10), and 10 trials of the final pair (CA × 10). Stage 2 consisted of five presentations of each of the pairs (e.g., [AB, BC, CA] × 5) in consecutive order. Stage 3 was divided into three blocks, where each block consisted of three presentation of each pair in consecutive order (e.g., [AB, BC, CA] × 3 for each block). In stage 4, each pair was presented once in consecutive order for nine trials (e.g., [AB, BC, CA] × 9). Lastly, stage 5 consisted of two blocks in which each pair was presented 18 times in a pseudorandom order for a total of 108 trials. If accuracy was below 50% on a given block, the block would repeat. The minimum number of trials completed in each training phase was 207.

2.4.2 Unitization training

Unitized training was identical to standard training with the following exceptions. Prior to commencing the training phase for each unitization condition, N.C. was shown three animations that highlighted the relations among the three stimuli for the current condition. Each animation depicted two of the three items interacting with one another such that a winner was made clear. The interactions were as follows: in one animation item A squished item B, in the second animation B stabbed C, and in the third animation C covered A. For each animation, the experimenter would describe the animation verbally and would ask N.C. to point to the object he felt would be the winner (e.g., "this object is squishing this other object, if you had to pick, which one do you think would be the winner?"). Following the presentation of the

Table 2
Overview of experimental sessions.

Sessions	Pre-test 1 − 2 Weeks	Pre-test 1 Month +	Training Standard	Training Unitized	Training Transfer	Test Immediate	Test 1-h Delay	Rationale
1			✓	✓		✓		Standard and unitized TP training and immediate test as in Ryan et al. (2013).
2	✓		✓	✓		✓	✓	Pre-test added following 1-week delay to examine retention of relations; inclusion of 1-h delay test to determine whether successful performance is due to online maintenance of relations, as in Ryan et al. (2013).
3–5	✓[a]	✓[b]	✓	✓		✓	✓	Pre-test to examine retention of relations; *a*- 1–2 week delay for sessions 4 and 5; *b*- 9 month delay for session 3, as NC was unavailable for testing during the school year.
6	✓		✓	✓	✓	✓	✓	Inclusion of transfer stimuli to determine if NC's intact performance on standard conditions was due to a generalization of the unitization strategy to novel stimuli.
7	✓		✓		✓	✓	✓	Additional novel stimuli and elemental tasks added to procedure to examine generalization of learning; unitized training removed to examine robustness of learning effect.
8–9	✓							1-week delay between prior testing sessions and current pre-test; all training removed to examine robustness of prior learning.
10		✓						Extended (1-month) delay between prior testing sessions and current pre-test; all training removed to examine robustness of prior learning.

three animations, N.C. completed the training blocks. The training blocks were identical to those used in the standard training, with the exception that a final still from each of the animations was presented centrally between the two items to remind N.C. of the animations and to encourage the formation of a fused or unitized representation. One unitized image (U) was presented on each trial and corresponded to the animation depicting the two items presented on the current trial (see Fig. 3).

2.4.3 Test phases

Unless otherwise noted, following each training phase, N.C. was tested immediately following training, and again following a 1-h delay. In the test phases, each pair of items was presented randomly four times for a total of 12 trials per test per condition. Test trials were identical to training trials with the exception that no feedback was given. The central unitized images were not presented in tests for the unitization conditions. Therefore, the same format was used for all tests in all conditions.

From the second session onward, N.C.'s retention of the relations from prior sessions was assessed with pre-tests, which were identical to the test blocks described above. Pre-tests were always administered at the beginning of the session. The RPS condition was never included in the pre-tests so as to not provide N.C. with hints regarding the overall problem structure. As in the immediate and delay tests, the pre-tests for the standard and unitization conditions had the same format.

In later sessions N.C.'s performance improved, such that he demonstrated intact performance on the unitization and, eventually, standard conditions on the pre-tests. In order to assess his ability to generalize the unitization strategy and/or learn novel relations following successful learning and retention with a unitization strategy, N.C. was trained on novel stimuli, referred to as the transfer conditions. Training in the transfer conditions was identical to training in the standard conditions. Lastly, we examined whether N.C.'s performance on the TP conditions would be disrupted following exposure to stimuli that were structured with a non-relational hierarchy of response contingencies as in the Geometric Shapes-Elemental condition. Training in the elemental condition was identical to the standard training, with the exception that the relationship underlying the stimuli formed a response hierarchy ($A>B>C$) rather than TP relations ($A+B-$, $B+C-$, $C+A-$). More details regarding the rationale for including these conditions are provided below in the context of N.C.'s performance.

In all phases, the side of presentation (left/right) for each object within each pair was counterbalanced, such that the correct item was equally presented on the left/right.

2.4.4 Description of sessions

An overview of the experimental sessions including the conditions tested, delays between sessions, and N.C.'s performance is shown in Table 3.

Sessions 1–6: Sessions 1–6 used our previously established procedure (Ryan et al., 2013) to contrast N.C.'s TP performance under standard and unitized conditions over training as well as on immediate and 1-h delay tests. N.C. was trained and tested on the following conditions in this order: RPS, Geometric Shapes, Abstract Objects, Geometric Shapes-Unitized, and Abstract Objects-Unitized conditions. N.C. was always trained and tested on the standard conditions before the unitization conditions, so as to not bias performance on the standard conditions with a generalized unitization strategy. Due to time constraints, N.C. was not tested following the hour delay in Session 1. Due to a computer error, N.C. was not shown the unitization animations in Session 2. Instead, the experimenter described the animations during Phase 1 of training, using the unitized-images for reference.

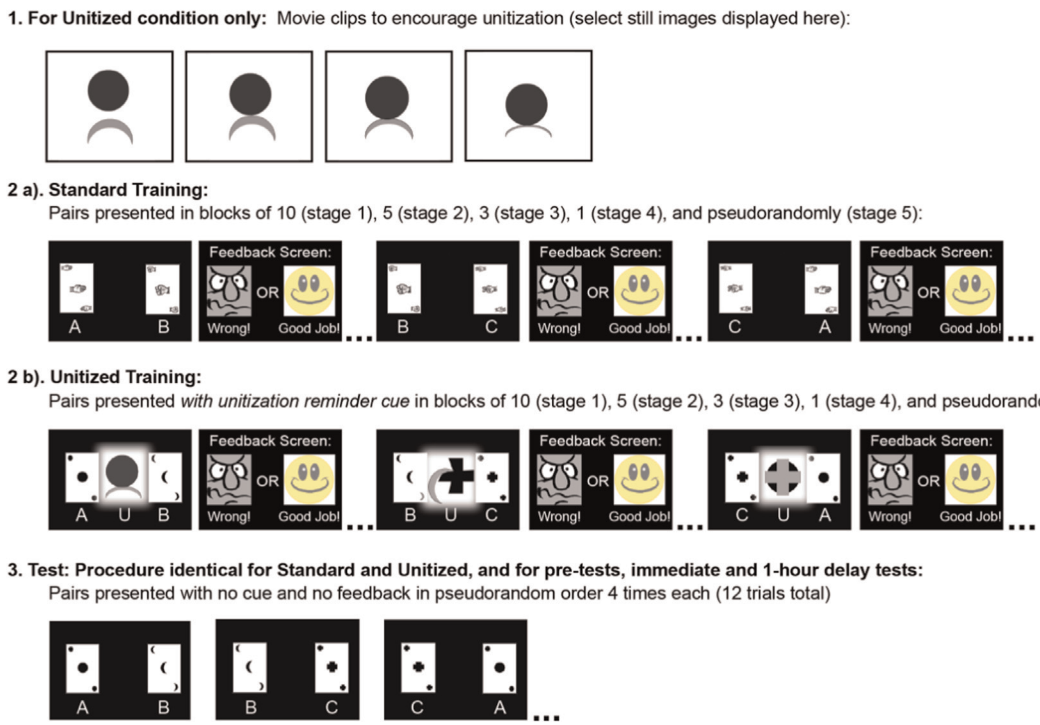

Fig. 3. Experimental procedures. (1) Example stills from the flash animations that were shown before training for the unitized condition. Flash animations depicted one object physically interacting with the other object with the relations of squish, pierce, or cover. (2) Training procedures: (a) Standard training (RPS, Shapes, and Elemental) presented two stimuli, one on each side of the screen, and participants were required to select the correct item that "wins". Responses were self-paced and feedback was provided. (b) Unitized training was identical to standard training except that a still image from the animations was included in the center of the stimulus display ("U") to serve as a "hint" for which stimulus was correct. (3) Test procedures. All tests blocks, regardless of whether training was standard or unitized, and regardless if the test was a pre-test, an immediate test, or occurred after an hour delay, followed the same procedure and the same stimulus arrangement. Note that the stimuli are shown by their corresponding letter (A–C, U) for ease of illustration; however, such letters were not presented to the participants. Figure adapted from Ryan et al. (2013).

In Sessions 2–6, N.C. was given pre-tests for the Geometric Shapes, Abstract Objects, Geometric Shapes-Unitized, and Abstract Objects-Unitized conditions before undergoing training.

Session 6 was identical to the prior sessions with the exception that in addition to the five original conditions, N.C. was also trained and tested on the Abstract Objects-Transfer #1. This first transfer condition was included to assess N.C.'s ability to transfer the unitization strategy to learn the relations among a novel set of stimuli. Training occurred in the following order: RPS, Geometric Shapes, Abstract Objects, Abstract Objects- Transfer #1, Geometric Shapes-Unitized, and Abstract Objects-Unitized.

Session 7: To preview the results from Session 6, N.C. demonstrated intact performance in the Abstract Objects-Transfer#1 condition, even following the 1-h delay. Given his intact performance, we further examined his ability to transfer learning to novel stimuli in Session 7. Specifically, we examined whether N.C. would learn novel relations in a session where he was not given training with a unitization strategy. N.C. was first given pre-tests on the previously trained standard and unitized TP conditions, as well as the transfer condition that he was trained on in Session 6 (Geometric Shapes, Abstract Objects, Geometric Shapes-Unitized, Abstract Objects-Unitized, and Abstract Objects-Transfer #1). Following the pre-tests, N.C. was trained and tested only on the remaining transfer conditions (Abstract-Objects-Transfer #2, Abstract-Objects-Transfer #3, Geometric-Shapes-Transfer #1, Geometric-Shapes-Transfer #2, and Geometric Shapes-Elemental condition).

Sessions 8–10: In Sessions 8–10, N.C. was given pre-tests on the 10 conditions from the prior sessions – the four original conditions excluding RPS and the six transfer conditions. In these final sessions, N.C. was not given pre-tests for the RPS condition, nor did he complete any training blocks. The order of condition pre-tests was varied in Sessions 8–10 and is listed in Table 3.

2.5. Descriptive statistics

In all training phases, N.C.'s mean accuracy and the number of trials required to complete training were measured. N.C.'s accuracy was measured on each of the test phases (pre-test, immediate test, and 1-h delay test).

To demonstrate that N.C. shows the typical pattern of impairments relative to controls (who do not show impairments), N.C.'s performance from the first testing session was contrasted against controls for the RPS, Geometric Shapes, and Abstract Objects conditions (see Fig. 4). The control participants are three groups of healthy young adults whose performance was initially reported in Ostreicher et al. (2010). These healthy controls differed in the experimental conditions they received. Participants in the Semantic group ($N=16$, $M_{Age}=22.4$ years, $SD_{Age}=3.3$ years, $M_{Education}=16.1$ years, $SD_{Education}=1.9$ years) completed two semantic conditions (RPS and a condition with the playing cards King, Ace, and Two, where the Ace could be high or low) followed by the Geometric Shapes and Abstract Objects conditions – this condition is most similar to the training N.C. received in his first testing session. Participants in the Alone group ($N=16$, $M_{Age}=23.5$ years, $SD_{Age}=3.1$, $M_{Education}=16.7$ years, $SD_{Education}=2.6$ years) only completed the Geometric Shapes and Abstract Objects conditions. Lastly, participants in the Practice group ($N=16$, $M_{Age}=19.5$ years, $SD_{Age}=1.2$, $M_{Education}=13.5$ years, $SD_{Education}=1.4$ years) completed two training and test blocks for each of the Geometric Shapes and Abstract Objects conditions, however only their performance in the first block of each condition is considered here. As is evident from Fig. 4, although N.C. performs similarly to controls on RPS, as he falls within the 95% confidence interval of the control

Table 3
Summary of experimental sessions, including the conditions tested and N.C.'s resultant performance.

Session	Figure	Description	RPS	Geometric Shapes - Standard	Abstract Objects - Standard	Geometric Shapes - Unitized	Abstract Objects - Unitized	Abstract Objects - Transfer #1	Geometric Shapes - Transfer #1	Abstract Objects - Transfer #2	Geometric Shapes - Transfer #2	Abstract Objects - Transfer #3	Geometric Shapes - Elemental
1	3	Immediate test	✓	✗	✗	✓	✗	–	–	–	–	–	–
		1-h delay test	–	–	–	–	–	–	–	–	–	–	–
2	3	Pre-test (8-day delay)	–	✗	✗	✓	✗	–	–	–	–	–	–
		Immediate test	✓	✓	✓	✓	✗	–	–	–	–	–	–
		1-h delay test	✓	✗	✗	✓	✓	–	–	–	–	–	–
			N.C.shows intact TP performance on immediate tests after using a working memory strategy-but only shows intact performance on unitized conditions following an hour delay										
3	3	Pre-test (9-month delay)	–	✗	✗	✗	✗	–	–	–	–	–	–
		Immediate test	✓	✗	✗*1*	✓	✓	–	–	–	–	–	–
		1-h delay test	✓	✗	✗	✓	✓	–	–	–	–	–	–
4	3	Pre-test (6-day delay)	–	✗	✗	✓	✗	–	–	–	–	–	–
		Immediate test	✓	✓	✓	✓	✓	–	–	–	–	–	–
		1-h delay test	✓	✓	✗	✓	✓	–	–	–	–	–	–
			N.C. shows intact performance on all conditions following a 1-h delay and intact performance on unitized conditions following a 6-day delay.										
5	3	Pre-test (7-day delay)	–	✗	✗	✓	✓	–	–	–	–	–	–
		Immediate test	✓	✓	✓	✓	✓	–	–	–	–	–	–
		1-h delay test	✓	✗	✓	✓	✓	–	–	–	–	–	–
			N.C. continues to shows intact performance on most conditions following a 1-h delay-introduced first set of transfer items in subsequent session.										
6	3	Pre-test (13-day delay)	–	✗	✓	✓	✓	–	–	–	–	–	–
		Immediate test*	✓	✗	✓	✓	✓	✓	–	–	–	–	–
		1-h delay test*	✓	✓	✓	✓	✓	✓	–	–	–	–	–
			N.C. shows intact performance on all conditions following a 1-h delay, including the standard conditions.										
7	3	Pre-test (9-day delay)	–	✗	✗	✓	✓	✗*1*	–	–	–	–	–
		Immediate test*	–	–	–	–	–	–	✓	✓	✓	✓	✓
		1-h delay test*	–	–	–	–	–	–	✓	✓	✗*2*	✓	✓
8	3 and 4	Pre-test (7-day delay)	–	✓	✗	✓	✓	✗	✓	✓	✓	✓	✗*3*
		Test order		1	2	4	5	3	6	7	9	10	8

Table 3 (*continued*)

Session	Figure	Description	RPS	Geometric Shapes - Standard	Abstract Objects - Standard	Geometric Shapes - Unitized	Abstract Objects - Unitized	Abstract Objects - Transfer #1	Geometric Shapes - Transfer #1	Abstract Objects - Transfer #2	Geometric Shapes - Transfer #2	Abstract Objects - Transfer #3	Geometric Shapes - Elemental
9	3 and 4	Pre-test (6-day delay)	–	✗	✗	✓	✓	*✗1*	✓	✓	✓	✓	*✗3*
		Test order		6	7	9	10	8	3	2	4	5	1
10	3 and 4	Pre-test (1-month delay)	–	✗	✓	✓	✓	*✗1*	✗	✓	✓	✓	*✗3*
		Test order		7	8	9	10	6	3	2	4	5	1

✓: intact; ✗: impaired; –: condition not tested.;
Highlights of results are noted within the table.
✗1 = reported reversal of relations (scored 0/12);
✗2 = reported reversed relations (scored 1/12);
✗3 = reported TP rules for Elemental Task;
* = test performance for transfer items presented in Table 5.

group's performance, he is impaired relative to the controls on the Shapes and Abstract conditions. Furthermore, healthy young adults show intact performance on standard versions of TP even in the absence of training with semantically rich stimuli, such as RPS, as is evident from performance in the Alone and Practice groups.

Overall, N.C. shows impairments learning novel arbitrary relations in TP relative to healthy controls, who do not show impairments (Hopf et al., 2013; Ostreicher et al., 2010). Beyond this initial comparison, which we include here to show N.C.'s initial impairments, we will not compare N.C.'s performance on the remaining sessions and conditions to healthy controls. Critically, our interest lies in how N.C.'s performance differs across standard, unitized and elemental versions of the task, across the various sessions. N.C.'s accuracy was also interpreted relative to the elemental threshold (0.67), separately for each condition, test, and session. The elemental threshold reflects the maximum score achievable if a winner-takes-all rule is incorrectly applied to a TP task, whereby an individual would have only correctly learned 2/3 of the relations. Therefore, N.C.'s performance was only classified as intact when it exceeded the elemental threshold and the 95% CI of his performance did not include 0.67. 95% confidence intervals (CI) were computed around N.C.'s mean accuracy in each condition for each session, for the training and test phases, to assess the reliability of N.C.'s performance relative to himself. The confidence intervals were calculated using the percentile method in R (v. 3.12) with the package *boot* (Canty and Ripley, 2014; Davison and Hinkley, 1997).

3. Results

N.C.'s accuracy and number of training trials as a function of condition and session are presented in Table 4, with 95% confidence intervals of his mean accuracy in each condition. Note that N.C.'s performance in the training phase was only impaired (i.e., the 95% confidence interval of his mean included the elemental threshold) in the Geometric Shapes and Abstract Objects conditions in Session 1. In Sessions 2–7, N.C. demonstrated intact performance during training for all conditions. As is noted below, N.C.'s intact performance during training is therefore at odds with his impaired performance in the test phases for the Geometric Shapes and Abstract Objects conditions.

N.C.'s accuracy on immediate tests, 1-h delay tests, and pre-tests for the original stimuli (RPS, Geometric Shapes, Abstract Objects, Geometric Shapes-Unitized, Abstract Objects-Unitized) are presented in Fig. 5, panels A–C, respectively. N.C.'s accuracy for the immediate and 1-h delay tests for the transfer stimuli are presented in Table 5 and his accuracy on pre-tests for all transfer stimuli are presented in Fig. 6. In all figures, the error bars represent bootstrapped 95% confidence intervals of N.C.'s accuracy. The dashed line in Figs. 4 and 5 represents the elemental threshold (0.67). As noted above, N.C.'s performance on any given TP condition was considered intact if his accuracy was above 0.67 and the 95% CI of his mean did not include 0.67.

Below we report N.C.'s performance across sessions for each condition as a function of the condition type (Standard/Unitized/Transfer). First we demonstrate that N.C. is similar to other amnesic cases, in that initially N.C. had intact performance with semantically rich stimuli (RPS), but impaired TP performance with standard training (Geometric Shapes, and Abstract Objects). Following this, we describe how, like D.A. (Ryan et al., 2013), N.C.'s test performance was supported by unitization training (Geometric Shapes-Unitized and Abstract Objects-Unitized). Lastly, we provide novel evidence of generalization of the unitization strategy, by showing that N.C.'s performance was intact on transfer conditions.

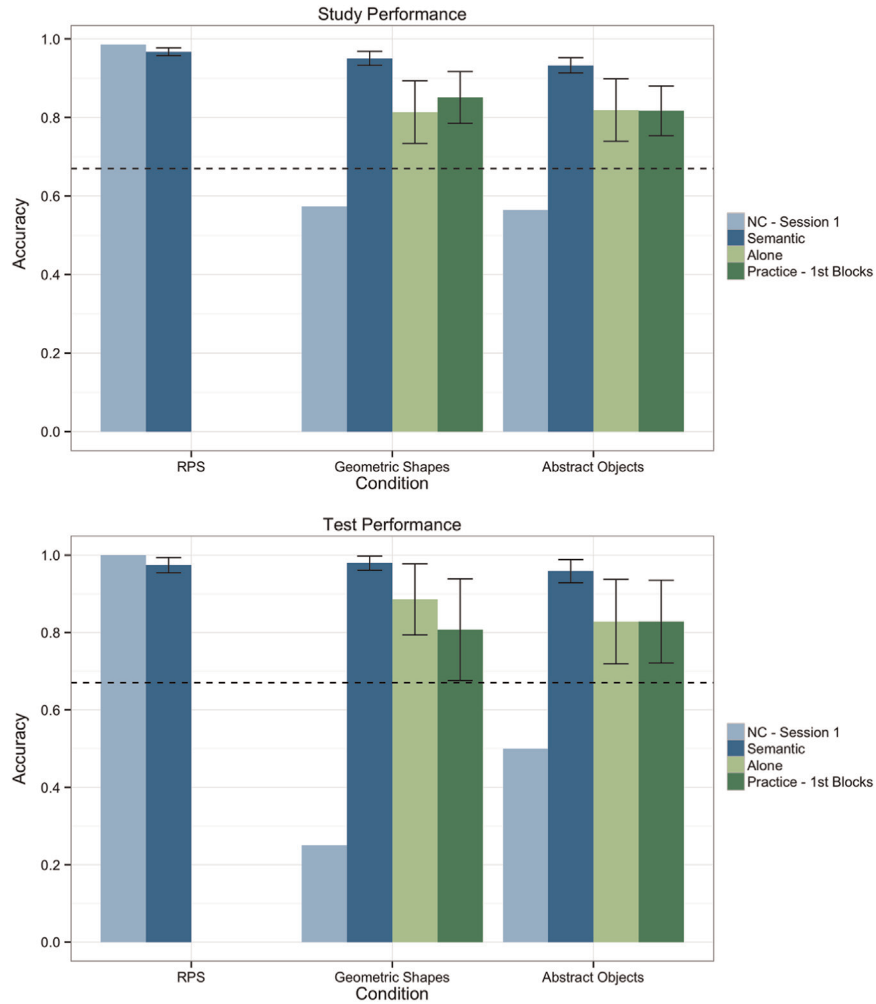

Fig. 4. Mean accuracy at study (top) and test (bottom) for N.C. (first session) and three groups of younger adults from Ostreicher et al. (2010) for the RPS, Geometric Shapes, and Abstract Objects conditions. Error bars represent the 95% confidence interval of the control's means. The dotted line here and in all graphs represents the elemental threshold (0.67 – see text for details).

3.1. *Intact RPS and impaired Standard TP*

N.C.'s performance on the RPS and Standard TP conditions in the initial sessions replicates our previous work with other amnesic cases (Moses et al., 2008; Ryan et al., 2013). N.C. demonstrated consistently high performance in the RPS condition both in the training phases (see Table 4) as well as in the test phases (see Fig. 3). In contrast to the intact performance observed in the semantically rich RPS condition, N.C. showed impaired performance in the standard TP conditions, as is typically observed in amnesic cases. Below are more detailed descriptions of his performance in these standard TP conditions, followed by a summary of these results.

3.1.1. *Geometric shapes*

N.C.'s performance in the Geometric Shapes condition was initially impaired, although it did gradually improved across sessions. N.C. was unable to learn novel relations in the initial sessions, replicating previous work (Rickard and Grafman, 1998). In Session 1, N.C. had trouble learning the relations during the training phase (accuracy = 0.57) and his performance was below the elemental threshold on the immediate test (see Table 4 and Fig. 5). In Session 2, N.C.'s performance improved during training (accuracy = 0.81) and on the immediate test (accuracy = 1.0), but he was unable to retain the relations over the 1-h delay (accuracy = 0.67). In this session, N.C. spontaneously reported using a working memory strategy for the first time, in which he continuously repeated aloud, "star beats trapezoid, trapezoid beats archway, archway beats star". Performance on the immediate and 1-h delay tests indicate that while this working memory strategy supported performance in the short term, it was ineffective for maintaining the relations over a longer delay.

In later sessions, N.C.'s performance during training and on the immediate tests gradually improved, but despite awareness that the shapes had "rock-paper-scissors-style rules", his 1-h delay test performance was intact only in Sessions 3 and 6. His pre-test performance was also impaired and variable – with intact performance only in Sessions 8 and 10. Note that N.C.'s variability, including extremely low pre-test scores in Session 4 (accuracy = 0.08) and Session 9 (accuracy = 0.17), potentially indicative of reversed relations, suggest that while he had a trend of improvements across sessions, he did not retain the exact relations, despite having had extensive training with feedback for these relations in Sessions 1–6.

3.1.2 Abstract Objects

N.C.'s performance on the Abstract Objects condition was quite similar to the Geometric Shapes condition, with initial impairments and slow, gradual improvements across the sessions. In Session 1, N.C. was impaired in the training phase (accuracy = 0.56) and on the immediate test (see Table 4 and Fig. 5). N.C.'s working

Table 4
Summary of N.C.'s training performance as a function of condition and session. Bootstrapped 95% confidence intervals for N.C.'s mean accuracy in parentheses.

Session	Description	RPS	Geometric Shapes	Abstract Objects	Geometric Shapes-Unitized	Abstract Objects-Unitized	Abstract Objects-Transfer #1	Geometric Shapes-Transfer #1	Abstract Objects-Transfer #2	Geometric Shapes-Transfer #2	Abstract Objects-Transfer #3	Geometric Shapes-Elemental
1	Accuracy	0.99 (0.97–1.00)	0.57 (0.51–0.64)	0.56 (0.50–0.63)	0.99 (0.98–1.00)	1.00*a* (0.99–1.00)	–	–	–	–	–	–
	Number of trials	207	246	216	207	207	–	–	–	–	–	–
2	Accuracy	1.00*b*	0.81 (0.75–0.86)	0.75 (0.69–0.81)	1.00*b*	1.00*b*	–	–	–	–	–	–
	Number of trials	207	207	216	207	207	–	–	–	–	–	–
3	Accuracy	0.99 (0.98–1.00)	0.77 (0.71–0.83)	0.75 (0.69–0.80)	1.00*b*	0.99 (0.98–1.00)	–	–	–	–	–	–
	Number of trials	207	216	225	207	207	–	–	–	–	–	–
4	Accuracy	1.00*a* (0.99–1.00)	0.84 (0.79–0.89)	0.87 (0.82–0.91)	1.00*b*	1.00*b*	–	–	–	–	–	–
	Number of trials	207	222	234	207	207	–	–	–	–	–	–
5	Accuracy	1.00*a* (0.99–1.00)	0.96 (0.93–0.98)	0.97 (0.94–0.99)	1.00*b*	1.00*b*	–	–	–	–	–	–
	Number of trials	207	207	207	207	207	–	–	–	–	–	–
6	Accuracy	0.99 (0.97–1.00)	0.90 (0.86–0.94)	0.99 (0.97–1.00)	1.00*a* (0.99–1.00)	1.00*a* (0.99–1.00)	0.89 (0.85–0.93)	–	–	–	–	–
	Number of trials	207	207	207	207	207	216	–	–	–	–	–
7	Accuracy							0.97 (0.94–0.99)	0.98 (0.96–1.00)	0.97 (0.94–0.99)	0.99 (0.98–1.00)	0.89 (0.85–0.93)
	Number of trials							207	207	207	207	207

a = mean accuracy rounded up to 1.00.
b = no errors therefore unable to calculate 95% CI.

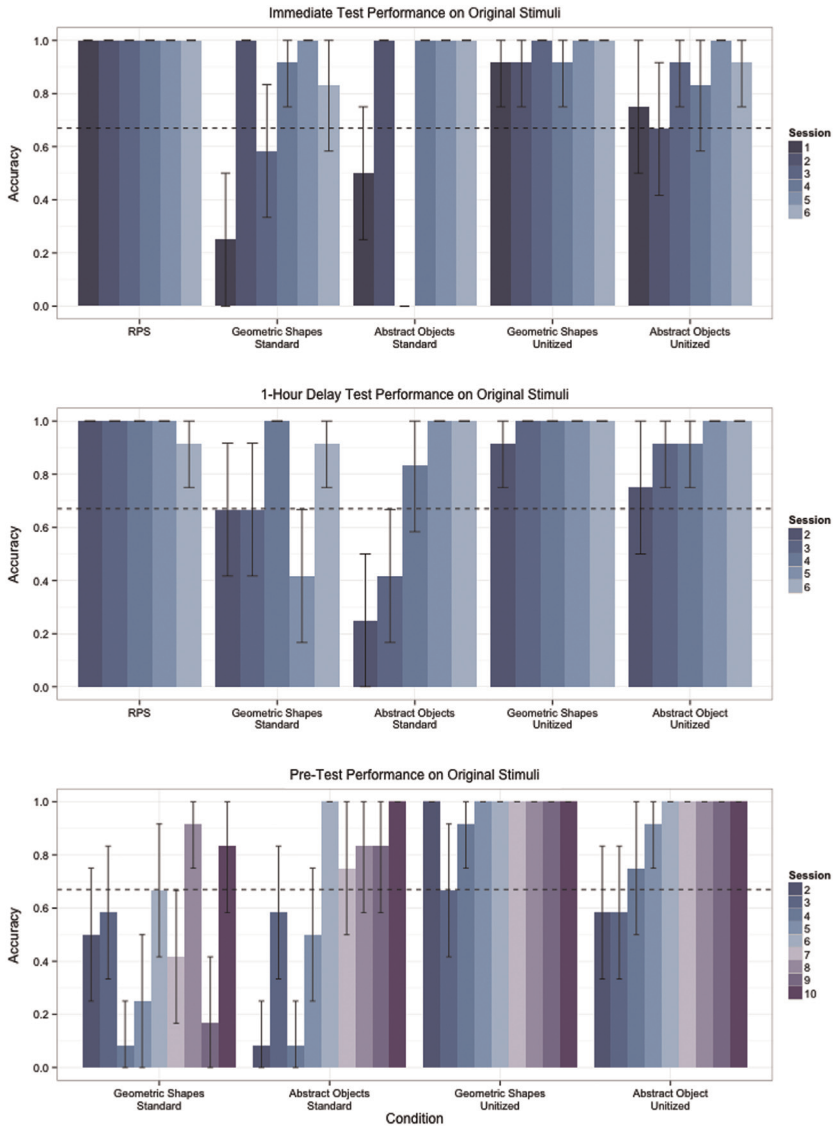

Fig. 5. Mean accuracy in the immediate test (A), 1-h delay test (B), and pre-test (C) phases of the TP tasks in the original conditions. Error bars represent the bootstrapped 95% confidence interval of N.C.'s mean.

memory strategy in Session 2, ("blob beats star, star beats robot, robot beats blob"), resulted in intact performance in training (accuracy=0.75) and the immediate test (accuracy=1.0), but not following a 1-h delay (accuracy=0.25).

N.C.'s performance improved in later sessions – with performance at ceiling on the immediate tests in Sessions 4–6, and on the 1-h delay tests in Sessions 5 and 6. Once again, although N.C. was aware that the items followed what he called "rock–paper–scissors-style rules", he did not always recall the exact rules for the Abstract Objects. In Session 3, he verbally reported the opposite set of relations and his accuracy was at floor performance (accuracy=0.00). The pre-tests showed a similar pattern of inconsistent behavior, with impaired performance in early sessions (2–5) and a trend of improved performance in later sessions, but with intact performance observed only in Sessions 6 and 10.

Overall, N.C.'s performance on RPS and the Standard TP

Table 5
Summary of performance on test phase as a function of transfer condition and session. Bootstrapped 95% confidence intervals of N.C.'s mean accuracy in parentheses.

Session	Description	Abstract Objects-Transfer #1	Geometric Shapes-Transfer #1	Abstract Objects-Transfer #2	Geometric Shapes-Transfer #2	Abstract Objects-Transfer #3	Geometric Shapes-Elemental
6	Immediate test	1.00*a*	–	–	–	–	–
	1-h delay test	1.00*a*	–	–	–	–	–
7	Immediate test	–	1.00*a*	1.00*a*	1.00*a*	1.00*a*	1.00*a*
	1-h delay test	–	1.00*a*	1.00*a*	0.08 (0.00–0.25)	1.00*a*	0.92 (0.75–1.00)

a=no errors therefore unable to calculate 95% CI.

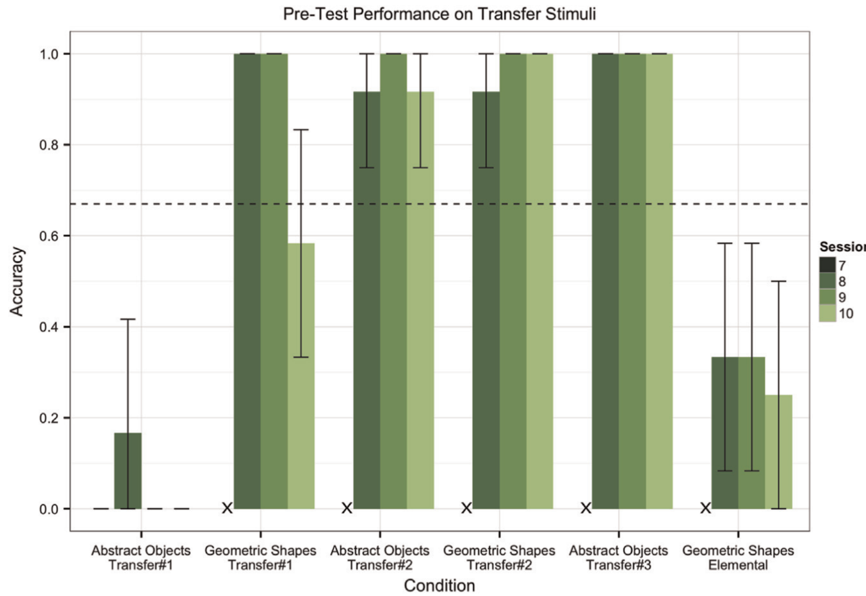

Fig. 6. Mean accuracy in the pre-test phases of the TP tasks in the transfer conditions. Error bars represent the bootstrapped 95% confidence interval of N.C.'s mean. Note that Session 7 only contained pre-tests for the original items and for Abstract Objects Transfer #1, for which N.C.'s accuracy was 0. Training for the remaining conditions occurred in Session 7, thus pre-tests for these conditions were administered starting in Session 8. X's indicate that no pre-test was administered in Session 7.

conditions replicates our prior work (Moses et al., 2008; Ryan et al., 2013), in that he showed intact performance in RPS and initially impaired performance in the Geometric Shapes and Abstract Objects conditions. Despite N.C.'s low scores on neuropsychological tests of working memory, he was able to successfully use a working memory strategy to support performance in the short term during training and the immediate tests. However, this strategy was not sufficient to support his performance over longer delays in the initial sessions. N.C.'s performance gradually improved across sessions in the Standard TP conditions. We hypothesize that N.C.'s improvements in later sessions were the result of increased successful learning with, and the transfer of, the unitization strategy, which we describe below. This hypothesis was later tested with the transfer materials, both when transfer items were presented in the same session as training with unitization (Session 6) and when these items were presented in a session where N.C. was not given any training with unitization (Session 7).

3.2. Intact TP performance through unitization

In contrast to his initially impaired performance on the Standard TP conditions, N.C. demonstrated rapid and consistent learning and expression of relations when given the unitization strategy. The benefit of unitization was more gradual in the Abstract Objects-Unitized condition than the Geometric Shapes-Unitized condition, but his performance in both of the unitized conditions was more consistent than in the Standard conditions over longer delays.

3.2.1 Geometric Shapes-Unitized

N.C.'s performance was consistently high in the Geometric Shapes-Unitized condition (see Table 4 and Fig. 5). In Session 1, N. C. had intact performance both in the training phase (accuracy = 0.99) and the immediate test (accuracy = 0.92). In Session 2, N.C.'s performance was intact even following a 1-h delay (accuracy = 0.92). His pre-test performance was also consistently high, where he showed intact performance in all pre-tests from Sessions 2–10, with the exception of Session 3, for which the pre-test occurred following a nine-month delay due to N.C.'s limited availability during the academic year.

3.2.2 Abstract Objects-Unitized

In Session 1, although N.C.'s performance was at ceiling during training (accuracy = 1.00), his performance was impaired on the immediate test when the central unitized images were removed (see Table 4 and Fig. 5). In Session 2, N.C.'s performance was impaired both on the immediate and 1-h delay tests (accuracy = 0.66 and 0.75, respectively), despite high accuracy during training. However, in Session 3, N.C. retained the relations across delays: his performance was intact on the immediate and 1-h delay tests, and it remained intact in Sessions 4–6. Over longer delays, N.C.'s pre-test performance was initially impaired (Sessions 2–4), but improved in later sessions (Sessions 5–10). Overall, despite his more gradual learning curve in the Abstract Objects-Unitized condition, N.C. learned and retained the relations in both unitized conditions within the initial six sessions. Importantly, N.C. showed lasting effects of this training over longer delays in the absence of any additional training with the unitization strategy (Sessions 7–10).

Overall, in contrast to the short-term benefits of the working memory strategy, unitization produced lasting benefits after longer delays. N.C. demonstrated intact TP performance in the Unitized conditions in earlier sessions than the Standard conditions, and was consistent in the relations he reported – N.C. never reversed the relations in the Unitized conditions.

3.3. Transfer of unitization to novel relations

By Session 5, N.C. demonstrated intact performance on the immediate tests for all conditions, intact performance on all 1-h delay tests with the exception of the Geometric Shapes condition, as well as intact pre-test performance for the two unitization conditions. Given N.C.'s intact performance with unitization, a first set of transfer stimuli was included in Session 6, and was presented immediately prior to training with the unitization strategy. Given that N.C.'s performance was better in the Abstract Objects condition than the Geometric Shapes condition in Session 5, the new stimuli selected for the transfer condition were abstract objects. N.C.'s performance on this transfer set (Abstract Objects-Transfer#1) was intact in training (accuracy = 0.89), and, critically, his performance was at ceiling for both the immediate and delayed tests following a single session of training (see Table 5).

To summarize, in Session 6, N.C. demonstrated intact learning of novel relations following a single session with standard training. This training session occurred in the same session as training with the unitization strategy. To further examine transfer of the unitization strategy to novel stimuli, N.C. was given training on additional sets of novel stimuli with previously unknown relations in Session 7, in the absence of same-session training with the unitization strategy. Overall, relative to the elemental threshold N.C. showed intact performance for all TP transfer conditions during training and the immediate test in Session 7 (Geometric Shapes-Transfer #1, Abstract Objects-Transfer #2, Geometric Shapes-Transfer #2, and Abstract Objects-Transfer #3 – see Table 4). Following this single training session, N.C. also showed intact performance on the 1-h delay tests in all of the new transfer conditions with the exception of the Geometric Shapes-Transfer#2 condition (see Table 5). In this latter condition, N.C.'s performance was at floor levels, again suggesting that he had reversed the relations, but had continued to respond using a set of TP rules.

Moreover, despite having had only one training session for each of the conditions, N.C.'s performance on the transfer conditions was generally intact over longer delays. N.C.'s pre-test performance in Sessions 8–10 (see Fig. 6) was consistently intact in the Abstract Objects-Transfer #2, Geometric Shapes-Transfer #2, and Abstract Objects-Transfer #3 conditions, even in Session 10, where there was a delay of over a month and half since his training on these conditions in Session 7. Note that Fig. 6 shows pre-test performance for the transfer conditions, where in Session 7 a pre-test was only administered for the Abstract Objects Transfer #1 condition, while in Sessions 8-10 pre-tests were administered for all conditions. N.C.'s performance in the Geometric Shapes-Transfer #1 condition was intact following one-week delays in Sessions 8 and in Session 9, but his performance was not intact following the longer delay when he was tested in Session 10. N.C.'s performance on the first set of transfer items (Abstract Objects-Transfer #1) was consistently at floor levels (see Fig. 5), suggesting that he had consistently reversed the relations.

N.C. was at ceiling on all tests and all delays in only one transfer condition-the Abstract Objects-Transfer#3 condition. Anecdotally, this was also the only condition in which he spontaneously reported using an elaborative processing strategy. In this condition, N.C. described an interactive "story" using the objects, and, importantly, his story and naming of the abstract objects was consistent across sessions. He described the story as "the spaceship tries to capture footage of the explosion with a camera. The camera gets footage of [the] explosion, [but] the explosion blows up [the] spaceship" (Session 9), where the spaceship refers to object A, the camera refers to object B, and the explosion refers to object C.

3.4. Elemental learning

In addition to training and testing on novel TP transfer conditions in Session 7, N.C. was also trained and tested on an elemental condition (Geometric Shapes-Elemental). This condition was included to assess whether N.C. would overgeneralize the unitization strategy and the TP rules to all testing conditions. Although his accuracy was numerically lower than in the TP conditions during training (accuracy=0.89), his performance was intact during training, relative to chance performance of 0.50 (see Table 4), and in both the immediate and 1-h delay tests (see Table 5). N.C. had a tendency to generalize the TP rules to this condition, stating at one point during the immediate test "I want to say that the task followed a rock–paper–scissors rule, but it isn't a rock–paper–scissors rule". Therefore, it appears that N.C. did not overgeneralize the application of TP rules and a unitization strategy to the elemental condition immediately following training in Session 7.

Despite N.C.'s intact performance for the Elemental condition in Session 7, his performance was consistently low over longer delays in the pre-tests, scoring around 0.33 in these later tests (see Fig. 6). This impaired elemental pre-test performance is consistent with a rigid and incorrect overgeneralization of TP rules to all conditions. Therefore, although N.C. was aware that the Geometric Shapes-Elemental condition did not follow the "rock-paper-scissors rules" in Session 7, by Session 8, he had forgotten that one of the conditions was different and reported using an RPS-like rule for all conditions.

In sum, N.C.'s intact performance on the novel stimuli in Sessions 6 and 7 suggests that he was able to transfer his learning to novel stimuli even after a single training phase, even when he was not given any unitization training in the same session (Session 7). Furthermore, N.C.'s performance was reliably high only for the stimuli for which he had a consistent, elaborate story, and for the stimuli that he named consistently across sessions. However, N.C.'s generalization of the unitization strategy to novel stimuli does not seem to reflect flexibility – N.C.'s over-generalization of these relations in the elemental task points to rigidity in this learning.

4. Discussion

Here we examined whether a developmental amnesic case, N. C., would benefit from a unitization strategy, similar to one that had been self-generated by another amnesic case, D.A., in a previous study (Ryan et al., 2013). In early sessions, N.C. showed a typical pattern of impaired TP performance in standard conditions but intact performance in a condition with semantically rich stimuli and relations (RPS), replicating our prior work (Moses et al., 2008; Ryan et al., 2013). Although N.C. appeared able to rely on a working memory strategy to support his performance on the immediate tests of the standard TP conditions, this strategy was ineffective at supporting performance over longer delays. In contrast, N.C. showed successful performance with the unitization strategy within the first few sessions, and his performance was supported by unitization over longer delays. Therefore, like D.A. (Ryan et al., 2013), N.C. showed successful learning and retention with unitization. The findings from N.C. on the unitized conditions highlight that the general strategy of unitization does not need to be self-generated to be effective, as N.C. did not spontaneously generate the strategy, but rather was taught the strategy experimentally through the videos and unitized stimuli during training. However, N.C.'s later intact performance on the transfer conditions does suggest that self-generation of the unitization strategy may allow for accurate performance to occur rapidly, with minimal training and/or sessions. Thus, while self-generation of unitization is not required to support performance, self-generation may impact the speed at which successful performance can be achieved. These results also suggests that two other cases, K.C. and R.F.R., who were tested with D.A., may not have benefited from unitization due to their more extensive cortical damage (Ryan et al., 2013). The patterns of spared and impaired TP performance in cases D.A. and now N.C. suggest that TP can be solved through an alternative method that is not dependent on intact functioning of the hippocampus and extended hippocampal system.

In contrast to D.A.'s selective improvement in the unitized conditions, N.C.'s performance also gradually improved in the standard conditions. N.C.'s improvements may reflect the extensive training received in the standard TP conditions and/or generalization of the unitization strategy to the standard conditions across sessions. The former explanation seems unlikely to account for all of N.C.'s improvements, given that in our previous work K.C. and R.F.R. showed no improvements in either the standard or unitized conditions after 8–10 sessions of training. Furthermore, although D.A. did benefit from a unitization strategy in the geometric shapes condition, his performance never improved in the standard abstract objects condition, and he required 11 sessions of training to show improvements in the abstract objects condition with the unitization strategy. D.A.'s relatively slower improvements in the Abstract Objects-Unitized condition, and his lack of improvements in the standard abstract objects condition are likely related to his volume reductions in perirhinal cortex. According to the Representational-Hierarchical model, the perirhinal cortex is an extension of the representational hierarchy in the ventral visual stream, and is where feature conjunctions come together to support fully specified representations objects (Bussey et al., 2002; Cowell et al., 2010a, 2010b). Given D.A.'s extensive volume loss in the perirhinal cortex, it may not be surprising that he had difficulties learning the relations among objects for which he did not have existing representations. Therefore, practice may help build up novel representations of the objects, and unitized representations of the objects interacting, however this practice would be specific to the training objects themselves.

To test whether N.C.'s improvements reflect generalization of the unitization strategy to standard conditions rather than simply specific practice effects that arise with repeated exposure to specific objects N.C. was tested on a series of transfer conditions. In these transfer conditions, N.C. was trained and tested on problem sets containing previously unseen geometric shapes and abstract objects. Despite being given only one training session for each condition, N.C. showed successful learning and long-term retention in three of the five TP transfer conditions. In one of the remaining two conditions (Abstract Objects-Transfer #1), N.C. consistently reported the reversed relations. These reversals were never corrected through feedback, as training was only given in Session 6, and although he was incorrect in the relations, he was consistent in the reversal. N.C. was at ceiling on all tests in only one transfer condition (Abstract Objects-Transfer #3), which was the only condition for which he told the same, elaborate story of the items interacting on all subsequent testing sessions. While we cannot rule out whether N.C. used additional strategies in the transfer conditions, the simplest explanation based on his performance on the standard and unitized conditions is that he generalized the unitization strategy to the novel stimuli. Overall, these results suggest that transfer of the unitization strategy is possible, providing the first evidence of transfer of TP learning in amnesia.

The present study also highlights the strength of unitization in producing rapid learning and long-term retention of novel relations in TP. This finding contributes to the sparse literature of transfer following memory rehabilitation in amnesia (Kaschel et al., 2002; Rose et al., 1999). The use of visual imagery, which we have previously hypothesized to be a component process of unitization (Ryan et al., 2013), has been associated with improved delayed recall (Cermak, 1975), and more recently has been shown to generalize beyond initial training sessions to aid individuals with memory impairments in remembering previously read information and prospective actions (Kaschel et al., 2002). Although our unitization strategy is still limited to lab-based tasks, N.C. showed transfer to novel, untrained stimuli, and this transfer occurred more rapidly than has been observed in prior work (e.g., Kaschel et al., 2002 had 30 90-min sessions). Taken together, unitization appears to be a viable strategy to support relational learning that can generalize beyond training materials.

N.C.'s pattern of performance on the transfer conditions also provides insight into the nature of his learning. While N.C. does show transfer to novel stimuli, the novel stimuli only differ from one another in surface features. The relational memory theory posits that the hippocampal-dependent memory system can support "… a relational form of representation exhibiting the critical property of flexibility, capable of being accessed and expressed in novel contexts; whereas procedural memory, operating independently of the hippocampal system, supports a fundamentally inflexible form of representation that can be expressed only in virtual repetitions of the initial learning situation." (Cohen and Eichenbaum, 1993, p. 49). Note that N.C.'s transfer occurred in conditions where, although the stimuli differed, the experimental context and training procedures were the same as those in prior training. Moreover, N.C.'s impaired performance on the Geometric Shapes-Elemental conditions pre-tests given in Sessions 8–10 suggests that he was not able to update his knowledge in a relational manner to inform when a rule-switch was appropriate. In other words, N.C. lacked the ability to form or update a relational representation containing information regarding the critical features that would otherwise indicate the appropriate context in which to use the unitization strategy and when the unitization strategy would not be appropriate for successful performance to occur. Overall, these findings show that while N.C.'s learning can support performance and transfer, his learning is still fundamentally inflexible.

The present findings can also be related to the configural association theory (Sutherland and Rudy, 1989) and the conjunctive learning theory (O'Reilly and Rudy, 2001). The configural association theory posits that the hippocampus is essential in the formation of configural or "blended" representations, representations that are described in a similar way to what we refer to as unitized representations. According to the configural theory, damage to the hippocampus or extended hippocampal system would result in the loss of the ability to form configural representations, which according to this theory are needed to solve TP. The finding that D.A. and N.C. can learn novel arbitrary relations in TP through unitization despite damage to their hippocampal/extended hippocampal system is at odds with the configural theory. However, the configural theory was updated to the conjunctive learning theory (O'Reilly and Rudy, 2001), and the conjunctive theory does posit that, given enough training, blended representations can be formed in the cortex in the absence of an intact hippocampus. For example these authors state that "the cortex will develop conjunctive representations over a relatively large number of trials… and can form complex conjunctive representations when given enough training trials (O'Reilly and Rudy, 2001, p. 321)." Therefore, the conjunctive theory can also account for the finding of intact learning through unitization in cases D.A. and N.C., depending on what is meant by "large number of trials" or "enough training trials". For a more in-depth discussion and comparison of the relational and conjunctive theories see (Moses and Ryan, 2006).

Findings from N.C. are consistent with those from D.A., and suggest that both individuals were was able to shift reliance away from using hippocampal-dependent relational binding to learn novel relations, and toward an alternative processing mechanism (Ryan et al., 2013). This alternative processing mechanism results in the formation and use of fused or unitized representations, which contain information about the novel relations. More specifically, these unitized representations are formed using visual imagery and action representations, are incorporated with information in semantic memory, and are strengthened through rehearsal and maintenance in working memory. Furthermore, high performance during training with the unitization strategy makes use of errorless learning (Glisky et al., 1986), which may support the strengthening of unitized representations. Information pertaining to the relations among items may then be derived online, through retrieval of the unitized representations and the interpretation of the actions contained therein.

Critically, unitization is a viable alternative strategy for relational learning in some amnesic cases, such as D.A. and N.C., as well as in healthy older adults (D'Angelo et al., 2014), as it likely circumvents hippocampally supported relational binding, and instead depends on a broad network of neural regions. An examination of the neural and cognitive profiles of the amnesic cases and older adults that do and do not benefit from unitization, along with prior work, helps us define the networks that support unitization. This network is hypothesized to be comprised of regions such as the anterior temporal lobes through interactions with the ventrolateral frontal cortex, which supports the incorporation of information into semantic memory (Noppeney et al., 2007), potentially through elaborative processing of the stimuli and the potential interactions among the stimulus pairs. The fused or unitized representations that are constructed based on currently presented information and incorporated with semantic knowledge through action representations may be supported by posterior visual cortices (Staresina and Davachi, 2010) and the precuneus (Cavanna and Trimble, 2006), and are maintained and manipulated on-line through frontal regions (Badre et al., 2010; Moscovitch and Winocur, 2002). Prior work in the associative recognition literature has also shown that both amnesic cases and older adults can show improvements in learning novel, arbitrary relations with strategies that encourage the fusion of items together (Kan et al., 2011; Quamme et al., 2007). These unitization effects in associative recognition memory have been related to differential patterns of activation in areas such as the perirhinal cortex (O'Neil et al., 2013) and a cluster of other areas more posterior along the ventral visual pathway (Staresina and Davachi, 2010).

Given the proposed network for unitization, it is likely that unitization was not an effective strategy for cases K.C. and R.F.R. due to extensive damage to their anterior temporal lobes, while unitization was effective for cases D.A. and N.C. as one or both anterior temporal lobes were intact, respectively. Consistent with this finding, we have recently shown that healthy older adults can also use unitization to alleviate age-related impairments in TP, but older adults who may be at risk for mild cognitive impairment (MCI) are unable to benefit from this strategy (D'Angelo et al., 2014). Early MCI is associated with volume loss in MTL structures, including anterior temporal regions (Khan et al., 2014; Schmidt-Wilcke et al., 2009). Therefore, it is possible that older adults at risk for MCI have early volume loss in anterior temporal regions and that this volume loss may be one reason why they are also unable to benefit from the unitization strategy. Although N.C. is much younger than the other amnesic cases tested to date, the finding that he benefits from unitization is unlikely to reflect an age effect, as we have recently shown that healthy older adults also benefit from unitization (D'Angelo et al., 2014).

Although N.C. does not appear to have damage to his hippocampal formation, he has reduced volumes in his right fornix and right mammillary body, as well as bilateral lesions to the medial superior thalamus, which appear to cover significant portions of his mediodorsal nuclei bilaterally and a small portion of his anterior nucleus on the right. Prior work has shown that the hippocampus is functionally related to the anterior thalamic nuclei, which receives direct hippocampal projections via the fornix, as well as indirect projections via the mammillary bodies (Aggleton and Brown, 1999; Aggleton et al., 2011). Beyond his impairments in the initial sessions of standard TP, N.C. has demonstrated impairments on standard tests of episodic memory function. Overall, N.C.'s pattern of damage suggests that his memory impairments are due to the functional relationship between the hippocampus and the extended hippocampal system. The differences in the patterns of pathology in individuals who do versus do not show learning benefits with unitization illuminates the brain–behavior relationship underlying unitization.

Unitization is a viable strategy to support relational memory impairments in amnesia, even when the strategy is not self-generated. We suggest that unitized representations consist of items that are fused through an action, are integrated with existing information in semantic memory; from these unitized representations, the relations among the distinct items may be derived. Training with unitization enables transfer and supports the subsequent learning and lasting retention of novel relations. Critically, the present findings emphasize the importance of replication when using the case study method to provide converging evidence for our understanding of cognitive processes, such as those involved in unitization, and the regions that support such processes (Rosenbaum et al., 2014).

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References

Aggleton, J.P., Brown, M.W., 1999. Episodic memory, amnesia, and the hippocampal–anterior thalamic axis. Behav. Brain Sci. 22, 425–444.

Aggleton, J.P., Dumont, J.R., Warburton, E.C., 2011. Unraveling the contributions of the diencephalon to recognition memory: a review. Learn. Mem. 18, 384–400. http://dx.doi.org/10.1101/lm.1884611.

Alvarado, M.C., Bachevalier, J., 2005. Selective neurotoxic damage to the hippocampal formation impairs performance of the transverse patterning and location memory tasks in Rhesus macaques. Hippocampus 15, 118–131. http://dx.doi.org/10.1002/hipo.20037.

Alvarado, M.C., Rudy, J.W., 1995. Rats with damage to the hippocampal-formation are impaired on the transverse-patterning problem but not on elemental discriminations. Behav. Neurosci. 109, 204.

Badre, D., Kayser, A.S., D'Esposito, M., 2010. Frontal cortex and the discovery of abstract action rules. Neuron 66, 315–326. http://dx.doi.org/10.1016/j.neuron.2010.03.025.

Bussey, T.J., Saksida, L.M., Murray, E.A., 2002. Perirhinal cortex resolves feature ambiguity in complex visual discriminations. Eur. J. Neurosci. 15, 365–374.

Bussey, T.J., Warburton, E.C., Aggleton, J.P., Muir, J.L., 1998. Fornix lesions can facilitate acquisition of the transverse patterning task: a challenge for "configural" theories of hippocampal function. J. Neurosci. 18, 1622–1631.

Canty, A., Ripley, B.D., 2014. Boot: Bootstrap R (S-Plus) Functions. R package version 1.3-13.

Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564–583. http://dx.doi.org/10.1093/brain/awl004.

Cermak, L.S., 1975. Imagery as an aid to retrieval for Korsakoff patients. Cortex 11, 163–169. http://dx.doi.org/10.1016/S0010-9452(75)80040-2.

Cohen, N.J., Eichenbaum, H., 1993. Memory. MIT Press, Cambridge.

Cowell, R.A., Bussey, T.J., Saksida, L.M., 2010a. Components of recognition memory: Dissociable cognitive processes or just differences in representational complexity. Hippocampus 20, 1245–1262. http://dx.doi.org/10.1002/hipo.20865.

Cowell, R.A., Bussey, T.J., Saksida, L.M., 2010b. Functional dissociations within the ventral object processing pathway. Cogn. Modul. Hierarchical Contin. 21373 (22), 2460–2479. http://dx.doi.org/10.1162/jocn.2009.21373 http://dx.doi.org.myaccess.library.utoronto.ca/10.1162/jocn.2009.21373.

D'Angelo, M.C., Smith, V.M., Kacollja, A., Zhang, F., Binns, M.A., Barense, M.D., Ryan, J.D., 2014. Aging and unitization: unitization supports relational learning in healthy older adults but not in those at-risk for MCI. Can. J. Exp. Psychol. 68, 263.

Davison, A.C., Hinkley, D.V., 1997. Bootstrap Methods and Their Applications. Cambridge University Press, Cambridge.

Driscoll, I., Howard, S.R., Prusky, G.T., Rudy, J.W., Sutherland, R.J., 2005. Seahorse wins all races: hippocampus participates in both linear and non-linear visual discrimination learning. Behav. Brain Res. 164, 29–35. http://dx.doi.org/10.1016/j.bbr.2005.05.006.

Eichenbaum, H., Cohen, N.J., 2001. From Conditioning to Conscious Recollection: Memory Systems of the Brain. Oxford University Press, New York.
Glisky, E.L., Schacter, D.L., Tulving, E., 1986. Learning and retention of computer-related vocabulary in memory-impaired patients: method of vanishing cues. J. Clin. Exp. Neuropsychol. 8, 292–312. http://dx.doi.org/10.1080/01688638608401320.
Hopf, L., Quraan, M.A., Cheung, M.J., Taylor, M.J., Ryan, J.D., Moses, S.N., 2013. Hippocampal lateralization and memory in children and adults. J. Int. Neuropsychol. Soc. 19, 1042–1052. http://dx.doi.org/10.1017/S1355617713000751.
Kan, I.P., Keane, M.M., Martin, E., Parks-Stamm, E.J., Lewis, L., Verfaellie, M., 2011. Implicit memory for novel associations between pictures: effects of stimulus unitization and aging. Mem. Cognit. 39, 778–790. http://dx.doi.org/10.3758/s13421-011-0071-6.
Kaschel, R., Sala, S.D., Cantagallo, A., Fahlböck, A., Laaksonen, R., Kazen, M., 2002. Imagery mnemonics for the rehabilitation of memory: a randomised group controlled trial. Neuropsychol. Rehabil. 12, 127–153. http://dx.doi.org/10.1080/09602010143000211.
Khan, U.A., Liu, L., Provenzano, F.A., Berman, D.E., Profaci, C.P., Sloan, R., Mayeux, R., Duff, K.E., Small, S.A., 2014. Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. Nat. Neurosci. . http://dx.doi.org/10.1038/nn.3606
Moscovitch, M., Winocur, G., 2002. The frontal cortex and working with memory. Princ. Front. Lobe Funct. . http://dx.doi.org/10.1093/acprof:oso/9780195134971.003.0012
Moses, S.N., Ostreicher, M.L., Rosenbaum, R.S., Ryan, J.D., 2008. Successful transverse patterning in amnesia using semantic knowledge. Hippocampus 18, 121–124. http://dx.doi.org/10.1002/hipo.20378.
Moses, S.N., Ryan, J.D., 2006. A comparison and evaluation of the predictions of relational and conjunctive accounts of hippocampal function. Hippocampus 16, 43–65. http://dx.doi.org/10.1002/hipo.20131.
Noppeney, U., Patterson, K., Tyler, L.K., Moss, H., Stamatakis, E.A., Bright, P., Mummery, C., Price, C.J., 2007. Temporal lobe lesions and semantic impairment: a comparison of herpes simplex virus encephalitis and semantic dementia. Brain 130, 1138–1147. http://dx.doi.org/10.1093/brain/awl344.
O'Neil, E.B., Barkley, V.A., Köhler, S., 2013. Representational demands modulate involvement of perirhinal cortex in face processing *Hippocampus*23, 592–605. http://dx.doi.org/10.1002/hipo.22117.
O'Reilly, R.C., Rudy, J.W., 2001. Conjunctive representations in learning and memory: principles of cortical and hippocampal function. Psychol. Rev. 108, 311–345.
Ostreicher, M.L., Moses, S.N., Rosenbaum, R.S., Ryan, J.D., 2010. Prior experience supports new learning of relations in aging. J. Gerontol. Psychol. Sci. 65B, 32–41. http://dx.doi.org/10.1093/geronb/gbp081.
Quamme, J.R., Yonelinas, A.P., Norman, K.A., 2007. Effect of unitization on associative recognition in amnesia. Hippocampus 17, 192–200. http://dx.doi.org/10.1002/hipo.20257.
Rickard, T.C., Grafman, J., 1998. Losing their configural mind. Amnesic patients fail on transverse patterning. J. Cogn. Neurosci. 10, 509–524.
Rickard, T.C., Verfaellie, M., Grafman, J., 2006. Transverse patterning and human amnesia. J. Cogn. Neurosci. 18, 1723–1733. http://dx.doi.org/10.1162/jocn.2006.18.10.1723.
Rose, F.D., Brooks, B.M., Attree, E.A., Parslow, D.M., Leadbetter, A.G., McNeil, J.E., Jayawardena, S., Greenwood, R., Potter, J., 1999. A preliminary investigation into the use of virtual environments in memory retraining after vascular brain injury: indications for future strategy. Disabil. Rehabil. 21, 548–554.
Rosenbaum, R.S., Gilboa, A., Moscovitch, M., 2014. Case studies continue to illuminate the cognitive neuroscience of memory. Ann. N.Y. Acad. Sci. 1316, 105–133. http://dx.doi.org/10.1111/nyas.12467.
Ryan, J.D., Althoff, R.R., Whitlow, S., Cohen, N.J., 2000. Amnesia is a deficit in relational memory. Psychol. Sci. 11, 454–461.
Ryan, J.D., Moses, S.N., Barense, M., Rosenbaum, R.S., 2013. Intact learning of new relations in Amnesia as achieved through unitization. J. Neurosci. 33, 9601–9613. http://dx.doi.org/10.1523/JNEUROSCI.0169-13.2013.
Saksida, L.M., Bussey, T.J., Buckmaster, C.A., Murray, E.A., 2006. Impairment and facilitation of transverse patterning after lesions of the perirhinal cortex and hippocampus, respectively. Cereb. Cortex 17, 108–115. http://dx.doi.org/10.1093/cercor/bhj128.
Schmidt-Wilcke, T., Poljansky, S., Hierlmeier, S., Hausner, J., Ibach, B., 2009. Memory performance correlates with gray matter density in the ento-/perirhinal cortex and posterior hippocampus in patients with mild cognitive impairment and healthy controls — a voxel based morphometry study. NeuroImage 47, 1914–1920. http://dx.doi.org/10.1016/j.neuroimage.2009.04.092.
Staresina, B.P., Davachi, L., 2010. Object unitization and associative memory formation are supported by distinct brain regions. Journal of Neuroscience 30, 9890–9897. http://dx.doi.org/10.1523/JNEUROSCI.0826-10.2010.
Sutherland, R.J., Rudy, J.W., 1989. Configural association theory: The role of the hippocampal formation in learning, memory, and amnesia. Psychobiology 17, 129–144.
Tombaugh, T.N., Kozak, J., Rees, L., 1999. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Archives of Clinical Neuropsychology : the Official Journal of the National Academy of Neuropsychologists 14 (2), 167–177.
Tombaugh, T.N., 2004. Trail Making Test A and B: normative data stratified by age and education. Archives of Clinical Neuropsychology : the Official Journal of the National Academy of Neuropsychologists 19 (2), 203–214. http://dx.doi.org/10.1016/S0887-6177(03)00039-8.